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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

NIAAA ADVANCES RESEARCH ON FETAL ALCOHOL SPECTRUM DISORDERS

In 1967, when French pediatrician Paul Lemoine first recognized that children with alcoholic mothers shared a pattern of abnormal facial features and behavior problems, he did not get much attention. Back then, conventional wisdom held there was nothing wrong with drinking during pregnancy. Most doctors never even raised the issue.

But today we know differently.

That's in part because, in 1973, pediatrician David Smith and researcher Kenneth Lyons Jones uncovered the same relationship that Dr. Lemoine did. Dr. Smith hoped to

bring more attention to the problematic pattern by giving it a name: fetal alcohol syndrome (FAS).

The name worked. Doctors, researchers, and the public in general began to pay more attention to FAS. Today, we have a much better understanding of the wide range of brain damage and developmental, cognitive, and behavioral problems caused by fetal alcohol exposure.

Research on this range of problems, which we now call fetal alcohol spectrum disorders (FASD), is a top priority for NIAAA. With our support, FASD research has already come a long way.

"Initially, some people thought that this problem only affected neglected children of poor alcoholic women who grew up in unfavorable postnatal environments—and that's why the kids did not look or behave like normal children. But NIAAA funded critical animal research studies that showed that alcohol is able to disturb the growth and development of an embryo or fetus," explained Sally Anderson, Ph.D., NIAAA.

Today, NIAAA supports researchers around the world who are making tremendous strides. In particular, current research is advancing more accurate diagnoses of FASD, distinguishing FASD from other disorders, and determining the prevalence of FASD with greater precision.

Accurate Diagnosis

Smith and Jones' original description of FAS has not changed very much. People with the following three features receive a diagnosis of full FAS:

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BRAIN SCANS REVEAL THE DAMAGE OF FETAL ALCOHOL EXPOSURE

PHOTO ESSAY

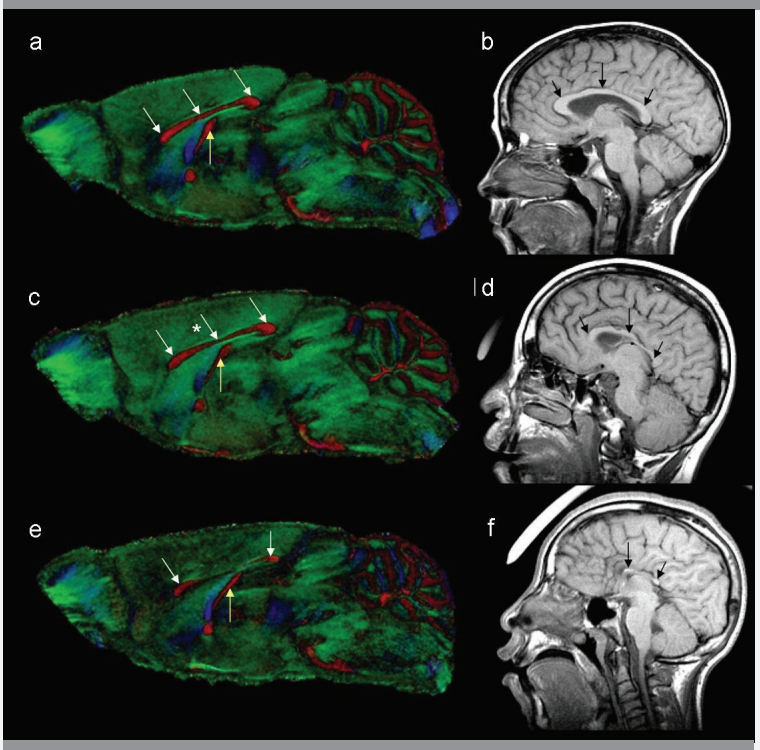
These images provide a closer look at how prenatal alcohol exposure can damage the brain. Magnetic resonance imaging (MRI) scans were taken of mice and humans with comparable amounts of alcohol exposure prior to birth. The scans reveal damage to structures that help the brain function properly (indicated by white and black arrows). One of these structures is the corpus callosum, which aids communication between the brain's two sides.

For the images on the left, researchers scanned the brains of mice that received different levels of alcohol during gestation. On the right are MRI brain scans of children known to have prenatal alcohol exposure comparable to those of the mice on the left.

The first mouse (a) was not exposed to alcohol, and its corpus callosum appears normal. A child without fetal alcohol syndrome (b) also has a normal corpus callosum.

The second mouse (c) received a moderate dose of alcohol on gestational day 7, which corresponds to late in week 3 of human prenatal development. This mouse has damage to the corpus callosum, particularly evident in a thinner middle section. A child with mild FAS (d) has comparable defects in the corpus callosum.

The third mouse (e) received a larger dose of alcohol on gestational day 7, and it shows a more severely reduced corpus callosum. This mouse also has damage to the hippocampal commissure (yellow arrows), another structure important to communication between the left and right sides of the brain. In a child with severe FAS (f), the corpus callosum is dramatically reduced in size.



MRI scans that show comparable amounts of brain damage associated with prenatal alcohol exposure. Mouse brains are shown on the left, and human brains are on the right.

Sources:
O'Leary-Moore SK, Parnell SE, Lipinski RJ, Sulik KK. Magnetic resonance-based imaging in animal models of fetal alcohol spectrum disorder. *Neuropsychology Review*, 2011 Jun;21(2):167–85.

Human MRI images are courtesy of Dr. S. Mattson.

FEATURE

IMAGING HELPS RESEARCHERS SEE INTO ALCOHOL-EXPOSED BRAINS

When it comes to understanding the effects of prenatal alcohol exposure on the brain, seeing is believing. Advances in imaging techniques are allowing researchers to get a fuller picture of how alcohol can affect the development of the brain's structure and, consequently, its functioning.

The imaging technique researchers use most often is MRI. In general, MRI uses a very strong magnet to create an image of any part of a person's body. But there are very specific types of MRI technology that are helping researchers shed light on different aspects of abnormalities caused by prenatal alcohol exposure, such as the following:

Structural MRI (sMRI) uses a strong magnetic field to distinguish between different types of brain tissue such as gray matter and white matter. By creating a contrast between tissues, sMRI allows researchers to measure the volume of brain structures and thickness of cortical tissue and compare measurements between different groups of people.

Diffusion tensor imaging (DTI) uses MRI technology to create an image of brain tissue by measuring the diffusion, or the direction of movement, of water molecules through brain tissues. In particular, DTI is helping researchers visualize and understand the changes that affect the structure of white matter fiber tracts during brain development.

Magnetic resonance spectroscopy (MRS) uses a strong magnetic field to measure the concentration of chemicals in the brain. This helps researchers understand the metabolic changes that take place in the brain. Researchers use MRS to compare healthy brains to brains exposed to alcohol prenatally.

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NIAAA ADVANCES RESEARCH...Continued from page 1

- Characteristic pattern of facial abnormalities;
- Growth deficits, either prenatally or postnatally; and
- Central nervous system dysfunction.

But fetal alcohol exposure does not always result in all three characteristics, meaning that some people would not receive an FAS diagnosis although they were adversely affected.

"Initially, clinicians were only able to identify individuals with FAS," explained Kenneth Warren, Ph.D., acting director of NIAAA, and a leading expert on FAS and FASD.

"If you didn't have the distinctive facial features, you weren't diagnosed with FAS. If you didn't have a growth deficit, you weren't diagnosed with FAS. Fortunately, our ability to understand and describe other areas has been enhanced and continues to improve," Dr. Warren said.

We now include a broader range of effects that result from prenatal alcohol exposure under the umbrella term of FASD. In addition to full FAS, FASD includes:

- *Partial FAS*, which describes people with some signs and symptoms of full FAS, but not all three.
- *Alcohol-related birth defects*, which include prenatal alcohol-induced physical abnormalities which affect vision, hearing, or the heart, kidneys, or skeletal structure.
- *Alcohol-related neurodevelopmental disorder* (ARND), which describes fetal alcohol-induced impairments to the growth and development of the brain or central nervous system, and/or the cognitive and behavioral problems of FAS without facial or growth abnormalities.

Distinguishing FASD From Other Disorders

Treating FASD effectively depends on an accurate diagnosis. Unfortunately, FASD are chronically under-diagnosed. The problem is that "distinguishing FASD from other developmental disorders is tricky, and evolving diagnostic standards are not yet accepted by everyone," explains Dr. Anderson.

Often, people with FASD are mistakenly diagnosed with conditions like attention deficit hyperactivity disorder (ADHD), which also causes learning and behavior problems.

Current research is making the differences between FASD and other disorders like ADHD much clearer. For example, we now understand the difference in a behavior called perseveration.

"Perseveration is an impaired ability to shift from one task to another. Many people with ADHD often switch from task to task constantly, but if you ask someone within the FASD spectrum to switch from one activity to another very quickly, they will likely be very resistant," explains Dr. Warren.

A recent review of research studies comparing children with FASD to children with ADHD concluded that children with ADHD have a harder time focusing and sustaining attention while children with FASD have a harder time shifting attention from one task to another and solving problems with flexibility. In addition, children with ADHD have trouble retrieving information they learn verbally. By contrast, children with FASD have trouble encoding and remembering verbally learned information. Other research suggests that stimulant medication, which often reduces inattention symptoms in children with ADHD, is not effective for children with FASD.

Prevalence

We know that FASD are the most common, preventable developmental disorders in the United States. Now, NIAAA is funding a new research study that will improve our knowledge of just how many people are affected by FASD. NIAAA is developing a network and infrastructure called Collaboration on FASD Prevalence (CoFASP) to test kindergarten and first-grade students for signs of FASD. Testing will begin with students in San Diego, California; Great Falls, Montana; Sioux Falls, North Dakota; and several communities in North Carolina.

"The new study will help determine the prevalence of FAS, partial FAS, and ARND, and also help the children in those communities get the special education services they need to thrive," said Dr. Warren.

Other Areas of Research

Clearly, research has come a long way since Dr. Lemoine's days. Yet Dr. Warren acknowledges there is still a lot we do not yet fully understand. The breadth of research continues to grow.

Other areas of significant NIAAA-funded research on FASD include demonstrating structural brain damage caused by prenatal alcohol exposure using advanced imaging, mitigating the extent of alcohol-related brain damage through nutrition, and understanding the effect of prenatal alcohol exposure on gene expression.

"Of course, our hope is that there will be a day when people no longer have FASD. But until that time, we will continue to try to understand these disorders as best we can. The more we know, the more we can improve the lives of individuals who struggle with these difficulties every day," said Dr. Warren.

Sources:
Coles, CD. Discriminating the effects of prenatal alcohol exposure from other behavioral and learning disorders. *Alcohol Research & Health*, Vol. 34(1), p. 47–48.

Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychology Review,* 2011, Vol. 21, p. 81.

IMAGING HELPS RESEARCHERS...Continued from page 2

Functional magnetic resonance imaging (fMRI) uses a strong magnetic field to show how blood flows in the brain. Generally, more blood flows towards an activated brain structure. Researchers can track this flow of blood to determine what part of the brain responds to particular stimuli and how different parts of the brain function. fMRI also allows researchers to track magnetically labeled blood, which follows a specific course within the brain.

MRI studies have helped scientists match up structural and functional brain deficits. For example, MRI helped Edward Riley, Ph.D., director of the Center for Behavioral Teratology and professor of psychology at San Diego State University, realize that children with FAS have significant deficits in the corpus callosum. This structure promotes communication between the left and right sides of the brain.

"Using MRI studies, we tracked a simple task," explained Dr. Riley. "We put kids' hands in a box so they couldn't see them. Then, we touched their fingers and asked them to tell us which fingers we touched."

The children could verbally identify the touched fingers on the hand the researchers actually touched. But when asked to point to the fingers that were touched on the opposite hand, "there were a lot more mistakes," said Dr. Riley.

By tracking the brain activity and resulting function with MRI, Riley's study showed "that [kids with FAS] have difficulty in transferring information from one hemisphere to another."

This advanced level of imaging has tremendous potential for helping researchers develop effective intervention and education strategies.

Source: Roussotte F, Soderberg L, Sowell E. Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: Evidence from neuroimaging. *Neuropsychological Review*, 2010 Dec;20(4):376–97. Epub 2010 Oct 28.

CHARTICLE

ONE IN EIGHT PREGNANT WOMEN DRINKS

On average, about 12 percent of pregnant women drink and about 2 percent binge drink (defined as 5 or more drinks on one occasion in the past 30 days). These rates have changed very little over time, according to a 2009 study by the Centers for Disease Control and Prevention that analyzed data from 1991 to 2005. Perhaps surprisingly, women who are older and more educated were more likely to drink during pregnancy than younger, less educated women. About 18 percent of pregnant women aged 35–44 reported drinking, compared with about 9 percent of pregnant women aged 18–24. About 14 percent of pregnant women with at least one college degree reported drinking, compared with about 8 percent of pregnant women with a high school diploma or less. The researchers speculate that the population of older women may include more who are dependent on alcohol, and that women with more education have more discretionary money to spend on alcohol.

Sources: Centers for Disease Control and Prevention. Alcohol use among pregnant and nonpregnant women of childbearing age: United States, 1991–2005. Morbidity and *Mortality Weekly Report*, 2009 May 22;58(19):529–32.

NEWS FROM THE FIELD

RECEPTOR MAY HELP EXPLAIN SUSCEPTIBILITY TO ADDICTION

Dopamine, a brain chemical that plays important roles in the control of normal movement and in pleasure, reward, and motivation, also plays a central role in substance abuse and addiction. In a new study conducted in animals, scientists found that a specific dopamine receptor, called D2, controls an organism's activity level and contributes to motivation for reward-seeking as well as to the rewarding effects of cocaine. A report of the findings, by NIAAA researchers, appears online in *Nature Neuroscience*.

In the study, scientists in NIAAA's Laboratory for Integrative Neuroscience worked with Argentinean researchers to develop genetically engineered mice in which expression of D2 receptors was selectively prevented in nerve cells that use dopamine as their neurotransmitter. The receptors normally present on these cells are known as D2 autoreceptors.

The researchers found that loss of D2 autoreceptors in the mice prevented the normal feedback effect by which dopamine already present in brain synapses reduces subsequent activity of dopamine-containing neurons and dopamine release. This control system prevents the neurotransmitter from reaching concentrations that produce excessive levels of movement and other behaviors. Mice that lacked D2 autoreceptors were more active than mice with normal autoreceptor levels. When investigators examined behaviors related to brain mechanisms of reward and addiction, they found that mice lacking D2 autoreceptors worked longer and harder to obtain food and showed increased sensitivity to the rewarding effects of cocaine, compared to normal mice. Cocaine increased activity in mice, and the mice lacking D2 autoreceptors were also more sensitive to this effect of the drug. The study may help explain why altered levels of D2 receptors in human

midbrain and striatum are associated with susceptibility to addiction.

The article abstract can be found here:

Cocaine supersensitivity and enhanced motivation for reward in mice lacking dopamine D2 autoreceptors.

http://www.ncbi.nlm.nih.gov/pubmed/21743470

NEWS FROM THE FIELD

HEAVILY ADVERTISED ALCOHOL BRANDS MAY ATTRACT MORE UNDERAGE DRINKERS

Underage alcohol use is a pervasive and persistent problem in the United States and many other countries, with serious health and safety consequences. Given the significant amount of alcohol advertising to which young people are exposed in virtually all types of media, scientists have sought to learn whether and how such advertising influences underage drinking.

In a study published in the *Archives of Pediatrics and Adolescent Medicine*, NIAAA-supported researchers asked 2,699 youth aged 16–20 about their alcohol use and alcohol brand preference as part of a long-term telephone survey of U.S. adolescents and media use. The researchers report that a majority of underage drinkers in the study identified a preference for a specific brand of alcoholic beverage, that the most-preferred brands included both distilled spirits and beer, and that brand preferences correlated with levels of brand-specific advertising expenditures. This correlation suggests that alcoholic beverage marketing efforts may be reaching and influencing underage audiences.

The researchers also found that young drinkers who identified a preferred brand also were more likely to engage

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HEAVILY ADVERTISED ALCOHOL BRANDS . . . Continued from page 5

in binge drinking. This finding highlights the need for further research to identify any causal connections between alcohol advertising, brand preferences, and binge drinking among underage youths.

Source:

Alcohol brand preference and binge drinking among adolescents. Archives of Pediatrics and Adolescent Medicine. 2011 Jul;165(7):675-6.

NEWS FROM THE FIELD

RESEARCH SHOWS THE ECONOMIC VALUE OF A MINIMUM LEGAL DRINKING AGE

Alcohol consumption and its harms are common among young people, including those who are below the minimum legal drinking age (MLDA) of 21. Researchers recently conducted economic analyses to estimate the effects of the MLDA on deaths, injuries, crime, and alcohol consumption, and to identify the costs and benefits of lowering the MLDA to 18. They report in the *Journal of Economic Perspectives* that a large body of evidence shows that setting the MLDA at 21 clearly reduces alcohol consumption and its major harms.

The researchers estimate that lowering the MLDA to 18 would result in an additional 8 deaths per 100,000 person years for the 18–20 age group. Using a common estimate of the value of a statistical life of $8.72 million, this suggests that for every 100,000 young adults allowed to drink legally during a year, the annual cost in terms of increased mortality would be about $70 million. The researchers also estimate that lowering the MLDA would impose additional costs on others for crime, health care, and deaths of nondrinking drivers and passengers of at least $12 million annually for every 100,000 newly legal drinkers. These estimates suggest that each drink consumed as a result of lowering the MLDA would generate harms valued at more than $15 to the drinker plus at least an additional $2.63 in harms imposed on others, all in addition to the purchase price of the drink.

According to the researchers, "… the evidence strongly suggests that setting the minimum legal drinking age at 21 is better from a cost and benefit perspective than setting it at 18 and that any proposal to reduce the drinking age should face a very high burden of proof."

The article abstract can be found here:

The minimum legal drinking age and public health.

http://www.ncbi.nlm.nih.gov/pubmed/21595328

NEWS FROM THE FIELD

EVIDENCE MOUNTS THAT BINGE DRINKING HARMS ADOLESCENT BRAIN DEVELOPMENT

Adolescents who drink alcohol often binge drink. While there is ample evidence that adolescent binge drinking increases risky behaviors and often results in negative consequences, we know less about the effects of alcohol on adolescent brain development. Now researchers have shown that the adolescent brain exposed to binge drinking responds differently when performing tests of working memory and spatial functioning compared to those of adolescents who do not binge drink. Previous research has linked impairments in memory and spatial functioning to alcohol dependence in adults.

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EVIDENCE MOUNTS THAT . . . Continued from page 6

In the current study, the researchers examined a sample of 40 adolescents between ages 16 and 19 who reported binge drinking at least once in the previous 3 months (binge drinking was defined as five or more drinks for males and four or more for females on at least one occasion). Using fMRI, the researchers examined blood flow to several brain regions as a measure of brain activation while the adolescents performed spatial working memory tests. The fMRI showed that adolescents who reported binge drinking exhibited different levels of regional brain activation compared to control subjects, suggesting alcohol-related differences in brain function.

When compared to the same gender controls, female adolescent binge drinkers exhibited reduced regional brain activation, while male adolescent binge drinkers exhibited equal or elevated regional activation. The reduced activation observed in females was correlated with poorer performance in sustained attention and working memory, while the increased activation in males was correlated with improved performance in spatial functioning. These data suggest there may be important gender differences in the impact of alcohol on the adolescent brain.

Overall, the findings suggest that the regions of the adolescent brain responsible for working memory and spatial functioning may be vulnerable to the physiological effects of binge drinking, with females potentially being more at risk than males. These effects could have implications for future behaviors extending into adulthood.

The article abstract can be found here:

Adolescent binge drinking linked to abnormal spatial working memory brain activation: Differential gender effects.

http://www.ncbi.nlm.nih.gov/pubmed/21762178

5 QUESTIONS WITH...

KENNETH WARREN, PH.D.

Dr. Warren is the acting director of NIAAA.

1. Why is FASD such an important research area for NIAAA?

Prenatal alcohol exposure is the leading preventable cause of birth defects and developmental disorders in the United States. The disabilities associated with FASD can persist throughout life and place heavy emotional and financial burdens on individuals, families, and society. So from a public health perspective, this is a serious and entrenched problem. Meanwhile, from a research opportunities perspective, studies continue to provide new insights into the nature of the disease and potential intervention and treatment strategies. Given the public health need and the potential of our research, FASD is an obvious priority area for us.

2. What important research advances have occurred since the first formal description of FAS was introduced in 1973?

I think we have made significant progress in three distinct areas. First, we have developed a much more comprehensive and nuanced understanding of the effects of prenatal alcohol consumption, and have refined our terminology to reflect this evolution. While we once had only a relatively simple understanding of FAS, we now recognize that drinking during pregnancy can lead to FASD, a full spectrum of neurobehavioral effects that range from intellectual and learning disabilities, poor executive function, and speech and language delays to behavioral and emotional difficulties, poor social skills, and motor deficits. This nuanced understanding helps researchers paint an accurate and realistic picture of the subtle complexities of these disorders as they search for better intervention strategies.

Second, researchers have made progress in understanding how alcohol damages the fetus (including epigenetic influences) and in the potential of preventing such damage through pharmacotherapeutic interventions during pregnancy. And finally, researchers are exploring new ways to use educational, behavioral, and nutritional interventions to improve or

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fully restore behavioral and cognitive functions in FASD patients.

Taken together, these research developments hold great promise for effective interventions that can help reduce the heavy burdens of FASD for patients and their families.

3. What are some of the ongoing challenges we face?

Despite the growing body of research evidence, too many pregnant women continue to drink, and many people still question whether alcohol consumption during pregnancy is a risky behavior at all. So finding effective and culturally relevant prevention and intervention strategies remains an elusive goal.

We also need to continue to improve our knowledge in areas where we have been making progress, such as developing tools to better identify all affected individuals and their unique patterns of alcohol-induced deficits. New technologies are proving to be extremely promising, such as the new three-dimensional imaging tools for detecting subtle facial characteristics associated with prenatal alcohol exposure. Yet we need to maintain our research focus and build upon these advances. That way, we can develop a range of tools to identify alcohol-related conditions quickly and provide appropriate medical and social services promptly.

We must also understand more fully how the quantity, frequency, and timing of alcohol exposure and maternal factors such as the mother's age, number of prior pregnancies, nutrition, and metabolism influence the development of FASD. Understanding the mechanisms underlying alcohol's detrimental effects, as well as the genetic and socioeconomic factors contributing to the risk for FASD, will allow researchers and clinicians to identify alcohol-related conditions more efficiently and develop more targeted and effective prevention and treatment strategies.

4. As our understanding of FASD continues to evolve, has it been difficult to keep stakeholders and the public apprised of all the research developments?

Perceptions can be difficult to change. But we are fortunate that a number of advocacy organizations, both in the United States and abroad, are dedicated to helping us bring research information to FASD stakeholders and the public. These organizations have been vital to the progress of FASD research and education. For example, in the United States, the National Organization on Fetal Alcohol Syndrome (NOFAS) and the FAS Community Resource Center have done a great job of increasing public awareness, mobilizing grassroots action, and serving as liaisons among the many FASD stakeholder communities. These organizations also educate patients, health care providers, and policymakers. And most of all, groups like these provide important feedback from the families of affected individuals, helping to improve our clinical and prevention efforts and the community programs we serve.

5. After 35 years, you have certainly made your mark in the alcohol field. Looking back, what other careers captured your imagination?

As a young man in the Bronx, I worked as a musician. Thinking back, continuing to play music in clubs would have also made for an interesting professional life.

Learn more about current FASD research in the most recent issue of *Alcohol Research & Health*, the NIAAA journal. A downloadable copy is available at http://pubs.niaaa.nih.gov/publications/arh341/toc34_1.htm.

ABOUT US

NIAAA Spectrum is NIAAA's first-ever webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences. Each issue includes feature-length stories, news updates from the field, charticles and photo essays, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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